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Chronic Myeloid Leukemia With Minor-bcr Breakpoint Developed Hybrid Type of Blast Crisis

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Although a breakpoint in the minor breakpoint cluster region (m-bcr) of the BCR gene is observed in about two-thirds of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia, this type of genomic rearrangement occurs very rarely in chronic myeloid leukemia (CML). We describe here the eighth case of m-bcr CML, and delineate unique clinical characteristics found in common to the 7 cases reported previously. Monocytosis with a low neutrophil/monocyte ratio resembling chronic myelomonocytic leukemia was the most striking feature of m-bcr CML. Splenomegaly and basophilia were not conspicuous in chronic phase. A high percentage of immature granulocytes and low neutrophil alkaline phosphatase score were the findings in common with classical CML. Lymphoid and myeloid blast changes have been observed at and shortly after presentation so far. We found a hybrid type of blast crisis in the course of m-bcr CML.Thus, m-bcr CML may be a definite subtype of CML, exhibiting distinct clinical characteristics. The presence of fusion product of m-bcr mRNA in an earlier myeloid cell may involve monocytic lineage in addition to myeloproliferative defects. Am. J. Hematol. 57:320–325, 1998. © 1998 Wiley-Liss, Inc.

Key words: BCR-ABL; minor BCR rearrangement; chronic myeloid leukemia; blast crisis; polymerase chain reaction

INTRODUCTION

In more than 95% of chronic myeloid leukemia (CML), there is the consistent presence of the t(9;22)(q34;q11) translocation, the Philadelphia (Ph) chromosome. The Ph chromosome was also found in about 10–20% of adult acute lymphoblastic leukemias (ALL), 2–5% of pediatric ALL, and in occasional cases of acute myeloid leukemia (AML), lymphoma, and myeloma [1–3]. In Ph^+ CML and about one-third of Ph^+ ALL, the breakpoints occur within the 5.8-kb region (the major breakpoint cluster region, M-bcr) located in the central part of the BCR gene on chromosome 22, and within the ABL oncogene located on chromosome 9. The BCR-ABL fusion gene thus formed produces an 8.5-kb mRNA translated into a 210-kDa BCR-ABL fusion protein ($p210^{BCR\text{-}ABL}$) [4,5]. The remaining two-thirds of Ph^+ ALL have a breakpoint located in the first huge intron of the BCR gene (m-bcr region) leading to a 7-kb mRNA, which produces 190-kDa fusion protein ($p190^{BCR\text{-}ABL}$) [6–8]. Some of the former group of ALL have been proposed to represent lymphoid blast crisis of undiagnosed CML, while the latter group is considered as Ph^+ de novo ALL.

Thus, breakpoint in the m-bcr region has been considered to occur in acute leukemias, and not to be a feature of CML. However, seven CML patients with m-bcr rearrangement have been reported so far. Here, we describe the eighth case of m-bcr CML, and the first with development of hybrid type of blast crisis. The unique clinical features found in common to m-bcr CML are discussed.

CASE REPORT

A 49-year-old man was admitted because of increasing dyspnea on effort. The patient had a history of aorto-

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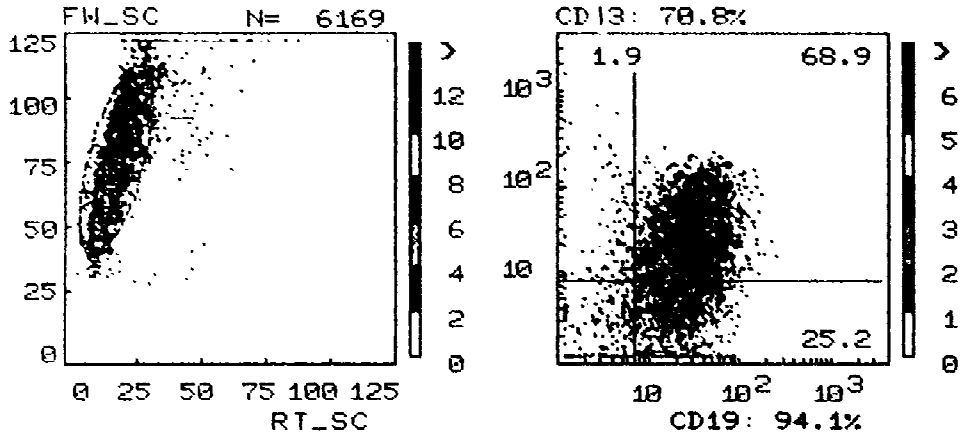

Fig. 1. Flow cytometric analysis of the leukemic cells at blast crisis. Left: Scatter cytogram gated the major population of the bone marrow cells. Right: The horizontal axis represents CD19, and the vertical axis CD13. Note the majority of the cells were $CD13^+CD19^+$.

coronary bypass operation performed 4 years earlier. He had been well until 1 month before admission, when he began to feel dyspnea. He consulted another hospital, where severe anemia with leukocytosis was disclosed, and was referred to our hospital after 4 U of blood transfusion. He had no palpable spleen, liver, or lymph nodes. His hemoglobin (Hb) was 9.0 g/dl, platelets 88 × 10^9/l, and while blood cells (WBC) 73.9 × 10^9/l with 9% blasts, 3% promyelocytes, 12% myelocytes, 1% metamyelocytes, 8% stabs, 29% segments, 1% basophils, 32% monocytes, and 14% lymphocytes. Serum iron was 206 μg/dl, ferritin 1,194 ng/ml, folic acid 3.8 ng/ml, vitamin B_{12} > 2,000 pg/ml, lysozyme 22.5 μg/ml, and LDH 951 U (I 16.5%, II 36.7%, III 27.2%, IV 11.2%, V 8.4%). The neutrophil alkaline phosphatase (NAP) score was 45. The bone marrow aspiration disclosed a nucleated cell count of 480,000/μl, megakaryocytes 56/μl, and M/E ratio 30.6 with 1.8% myeloblasts, 4.8% promyelocytes, 9.4% myelocytes, 17.4% metamyelocytes, 23.4% stabs, 16.0% segments, 0.2% eosinophils, 0.4% basophils, and 17.6% monocytes. Some dysplastic features in erythroid and myeloid series were observed. The results of flow cytometric analysis of the bone marrow aspirate with the whole-cell gate were as follows: CD5 1.3%, CD7 2.2%, CD11b 42.1%, CD13 82.5%, CD14 14.9%, CD19 10.0%, CD33 78.8%, CD34 21.1%, CD41 0.7%, and HLA-DR 50.1%. The cytogenetic study on the same material revealed a 46XY karyotype with a t(9,22)(q34,q11) translocation in 100% (20/20) of the cells. The results of genotypic analyses including Southern blot analysis, FISH, and PCR are detailed in Results.

Administration of hydroxyurea was successful only for cytoreduction. WBC was reduced to 10.3 × 10^9/l within 5 weeks. However, the differential was gradually shifted to the early stage of differentiation. Blasts were 57%, promyelocytes 2%, myelocytes 4%, metamyelocytes 1%, stabs 7%, segments 11%, monocytes 4%, and lymphocytes 14%, when hydroxyurea was abandoned. The bone marrow aspiration performed on the same day revealed 80.4% blasts in the normocellular background. Monocytes were almost depleted. The results of the flow cytometric analysis with the mononuclear cell gate were as follows: CD5 3.1%, CD7 5.3%, CD10 90.5%, CD11b 1.3%, CD13 70.2%, CD14 1.8%, CD19 92.0%, CD20 2.4%, CD21 13.1%, CD33 25.5%, CD34 86.5%, CD41 0.7%, HLA-DR 90.7%, and PCA-1 1.3%, and 59.2% of the cells were TdT positive. $CD13^+CD19^-$, $CD13^+CD19^+$, and $CD13^-CD19^+$ cells accounted for 1.9%, 68.9%, and 25.2%, respectively (Fig. 1). The majority of the cells were co-positive for both CD13 and CD19. Genotypic analyses were performed to confirm the lymphoid nature of the blasts (see Results). No additional chromosomal abnormality was detected.

After hybrid type of blast crisis was diagnosed [9], he was treated with several combinations of vincristin, cyclophosphamide, daunorubicin, cytosine arabinoside, and prednisolone, and received a bone marrow transplantation from his HLA-identical sister.

MATERIALS AND METHODS

Southern Blot Analysis

DNA samples were isolated from bone marrow or peripheral blood, digested with restriction enzymes, and subjected to Southern blot analyses. For the detection of M-bcr rearrangement, the 5′-probe (Bgl II-Hind III fragment covering subregion 0) and 3′-probe (Hind III-Bgl II fragment covering subregion 3) were used [10]. For the detection of rearrangements of T-cell receptor and immunoglobulin genes, appropriate probes were employed as described previously [11].

FISH

The bone marrow aspirates were processed with a Dual Color Chromosome in situ kit (Oncore, Gaithers-

burg, MD). As m-bcr/abl translocation DNA probe detects all bcr/abl translocations, we observed the real m-bcr/abl translocation by subtracting positive cells with the M-bcr/abl probe.

PCR

We used a highly sensitive nested PCR procedure for the detection of bcr/abl mRNA as described previously with some modification [12]. Briefly, total cellular RNAs were isolated from bone marrow aspirate. One microgram of cell line RNA was used as the standard template for the amplification reactions and one tenth of the total RNA sample from 1×10^7 white blood cells was used in the PCR analysis. The synthetic oligonucleotide sequences were as follows: BCR1 (5′-GCTTCTCCCT-GACATCCGTG-3′, nucleotide position 3208–3227) was the 5′ primer homologous to an M-bcr exon 2 (BCR exon 13) sequence, and BCR2 (5′-GGAGCTGCAGAT-GCTGACCAAC-3′, 3227–3248) was the 5′ primer located downstream of BCR1. BCR3 (5′-CGCATGTTCC-GGGACAAAAGC-3′, 1677–1697) was the 5′ primer on the BCR exon 1, and BCR4 (5′-CGCTCTCCCTCG-CAGAACTC-3′, 1698–1717) was the 5′ primer located downstream of BCR3. ABL1 (5′-GGCCCATGGTAC-CAGGAGTG-3′, 520–539) was the 3′ antisense primer homologous to an ABL exon 2 sequence, and ABL2 (5′-GTTTCTCCAGACTGTTGACTG-3′, 500–520) was the 3′ antisense primer located upstream of ABL1. ABL3 (5′-CATCTGACTTTGAGCCTCAG-3′, 248–267) was the 5′ primer on the initial part of ABL exon 2, and ABL4 (5′-GGTCTGAGTGAAGCCGCTCG-3′, 268–287) was the 5′ primer downstream adjacent to ABL3, which were used as internal control for mRNA quality, yielding a 253-bp product after amplification [13,14]. BCR1, BCR3, and ABL3 were used in the first PCR step together with ABL1 for detecting major and minor bcr breakpoints, and control, respectively. Then, each product of the first reaction was amplified with BCR2, BCR4, and ABL4 as the second PCR step together with ABL2. A 446-bp fragment is expected when the M-bcr exon 3 (BCR exon 14) is linked to ABL exon 2 (b3a2), and a 371-bp fragment when M-bcr exon 2 (BCR exon 13) is linked to ABL exon 2 (b2a2). Amplification of chimeric mRNA of BCR exon 1 and ABL exon 2 yields a 472-bp product (e1a2).

cDNA was synthesized using Moloney murine leukemia virus reverse transcriptase (BRL, Gaithersburg, MD) according to the manufacturer's protocol. The reaction mixture was adjusted to a volume of 50 μl and incubated for 40 min at 42°C. One-third of the final product was used as the template for amplification.

Each amplification template was made up to a volume of 100 μl containing 200 μmol/l of each deoxynucleotide triphosphate, 2.5 U of Taq polymerase (Roche, Tokyo, Japan), 1.5 mM $MgCl_2$, 50 mM KCl, 10 mM Tris pH 8.3, 0.01% gelatin, and 10 pmol of each specific amplification primer. Amplification cycles were repeated 30 times using a programmable heat block (Cetus, Emeryville, CA). Two consecutive amplification steps were performed, using 2% of the first PCR product as template for second amplification step. Ten microliters of each reaction mixture was run on composite gels containing 1.5% agarose in Tris/boric acid/EDTA (TBE) buffer. Gels were stained with ethidium bromide and photographed.

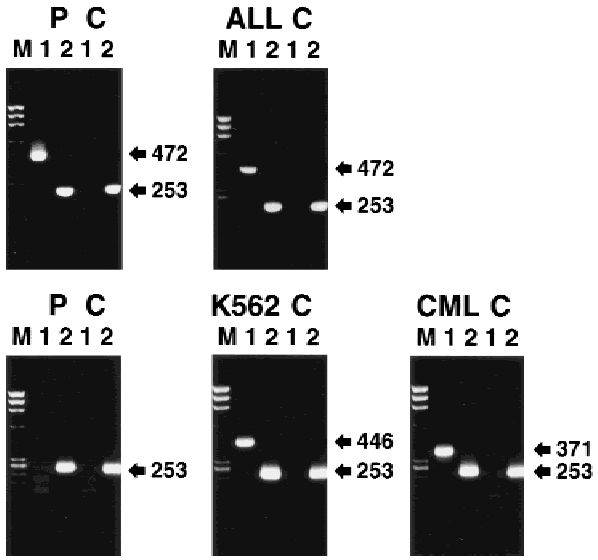

Fig. 2. Detection of BCR-ABL RNA transcripts by nested RT-PCR. P: patient; C: control; K562: a cell line with b3a2 type M-bcr breakpoint; CML: a classic CML patient with b2a2 type breakpoint; ALL: an ALL patient with known e1a2 type breakpoint. The BCR-ABL chimeric amplificate was run on lane 1. The ABL mRNA was amplified to check the process of the PCR, and was run on lane 2. Top: The primers were designed to amplify m-bcr rearrangement. Discrete 472-bp amplificate was clearly shown in lane 1 of the patient. Bottom: The primers were designed to amplify M-bcr rearrangement. No specific signal was detected in lane 1 of the patient.

RESULTS

Southern blot hybridization of BamH I and Bgl II digested DNA with probes covering M-bcr detected only germline configuration (data not shown). In accordance with this, the FISH study using the M-bcr/abl probe yielded negative results (5 positive cells out of 103 cells in interphase), while 104 out of 116 cells in interphase was positive for m-bcr/abl translocation.

The failure to amplify any BCR-ABL chimeric fragments also indicates the absence of a breakpoint in M-bcr (Fig. 2, bottom). Namely, no apparent amplificate was detected within the cDNA in RT-PCR with the primers corresponding to M-bcr exon 2 and ABL exon 2, while control K562 and another CML with an M-bcr break-

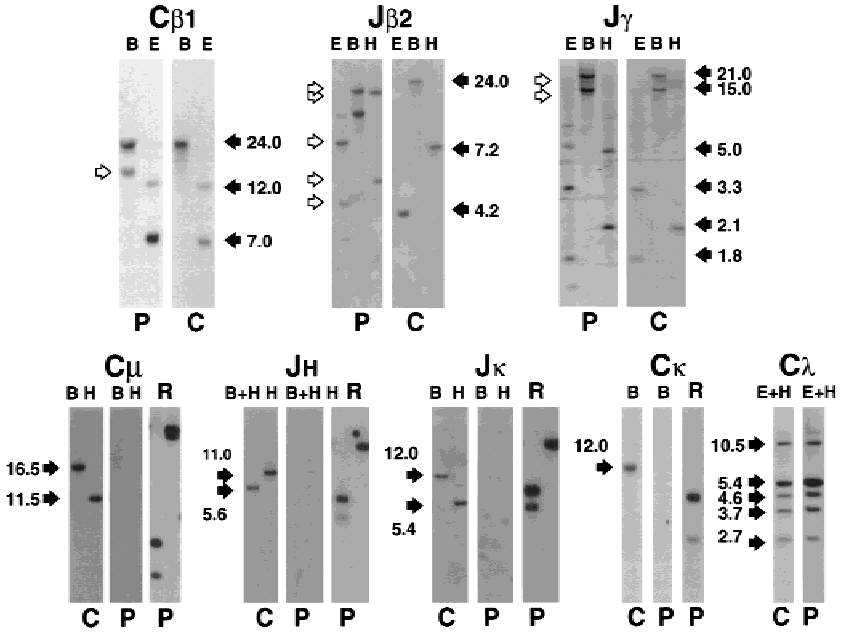

Fig. 3. Southern blot analyses performed to define the lineage of the leukemic cells. $C_{\beta1}$, $J_{\beta2}$, J_{γ}, C_{μ}, J_H, J_{κ}, C_{κ}, and C_{λ} are probes hybridized. B: BamH I, E: EcoR I, H: Hind III; R: re-hybridization with an irrelevant probe; C: germline control; P: patient. Black arrows: germ line bands; white arrows: rearranged bands.

point exhibited specific 446-bp (b3a2) and 371-bp (b2a2) signals, respectively. Another control 253 bp amplificates with primers within the ABL exon 2 and the absence of the specific signals from controls confirmed the successful process of this nested RT-PCR. On the other hand, PCR amplification primed with the primers spanning the sequence on the BCR exon 1 and ABL exon 2 revealed a 472-bp chimeric signal in the patient, showing a transcript derived from e1a2 junction (Fig. 2, top). This PCR product was identical in size to that obtained by the amplification of a known e1a2 m-bcr ALL cDNA.

Because the leukemic cells in the blast crisis exhibited phenotypically hybrid characteristics ($CD10^+$, $CD13^+$, $CD19^+$, $CD33^+$, HLA-DR^+, and TdT^+) (Fig. 1), Southern blot analysis was performed to confirm the hydrid nature of the blasts. EcoR I, BamH I, and /or Hind III digests of DNA extracted from the patient's bone marrow aspirate showed rearrangement bands using the $C_{\beta1}$, $J_{\beta2}$, and $J_{\gamma1}$ probes for T-cell receptor β and γ chain genes. As to immunoglobulin genes, these digests showed deletion patterns using J_H, C_{μ}, C_{κ}, and J_{κ} probes, while the λ chain gene exhibited germ-line configuration. The deletions of these specific genes were confirmed by re-hybridization with irrelevant probes (Fig. 3).

DISCUSSION

We described a Ph^+ CML case with an m-bcr breakpoint (m-bcr CML), presenting unique clinical features. Peripheral blood and marrow pictures on admission showed conspicuous monocytosis with a low neutrophil/monocyte ratio in addition to absence of basophilia, suggesting CMMoL rather than CML. Furthermore, because of the absence of splenomegaly, anemia, thrombocytopenia, high serum levels of vitamin B_{12} and lysozyme, and low NAP score, we could not make the diagnosis immediately. Although the classical Ph^1 chromosome was present, both Southern blot analysis and FISH failed to detect a breakpoint in the classical M-bcr region. Nested RT-PCR revealed a chimeric transcript in which the first exon of BCR is fused to the common exon 2 of ABL (e1a2), instead of that of the conventional b2a2 or b3a2 junction. This was further confirmed with FISH with the probe covering m-bcr. Thus, we diagnosed the patient as having rare m-bcr CML.

Because breakpoints in m-bcr are found in two-thirds of Ph^+ ALL, rearrangements of m-bcr have been assumed to occur exclusively in early lymphoid cells and to represent primary acute, rather than a chronic leukemic process. However, in addition to the present report, seven cases of m-bcr CMLs have been reported in the literature [15–21]. Their clinical features are summarized in Table I. Including one case, a diagnosis of ab initio ALL (L1) with common ALL immunophenotype [21], all cases exhibit the chronic myeloproliferative process distinct from ALL, demonstrating that such a strict correlation is not absolute.

Rare but accumulating cases make a hazy clinical entity more and more definite. As shown in Table I, these m-BCR CML patients share common features, some of which are not typical of classical CML. They lack marked splenomegaly at presentation in chronic phase, and demonstrate conspicuous monocytosis and a relatively low neutrophil/monocyte ratio, which resemble CMMoL as described by Melo et al. [3,19]. On the other

TABLE I. Clinical and Hematological Features of m-bcr CML Patients*

	Selleri et al. [15]	Zaccaia et al. [16]	Nakamura et al. [18]	Melo et al. [19]	Guo et al. [20]	Costello et al. [21]	Ohno et al. (present case)
Sex/age	F/44	F/77	M/65	F/81	M/52	F/32	M/49
Presentation	CP	CP~AP	AP	CP	CP	ALL~CP	CP~BC
Splenomegaly	−~+	−~++	+++	−~−	+	−	−
Karyotype	46XX, t(9;22)	46XX, t(9;22)	46XX, t(9;22)	45X, t(9;22)	46XX, t(9;22)	46XX, t(9;22)	46XX, t(9;22)
NAP score	Low	Low	Low	110~22	ND	ND	33~82
Platelets ($\times 10^9$/l)	510	261	ND	335	187	77[a]	88
WBC ($\times 10^9$/l)	56.8	63.3	174.4	32.5	180	4.5[a]	73.9
Monocytes (%)	12	4	22	19.9	6	6[a]	32
($\times 10^9$/l)	6.8	2.5	38.3	6.5	10.8	0.27[a]	23.6
Basophils (%)	2	1	4	0	13	1[a]	1
($\times 10^9$/l)	1.1	0.6	7	0	23.4	0.045[a]	0.74
Neutrophil/monocyte	5.3	12.5	1.8	3	8.3	2.5[a]	0.88
Immature granulocytes (%)	19	38	27	16	24	27[a]	25
Observation	5 years	2 years	ND	2 years	20 months	16 months	1.5 years
Follow-up	Treated αINF Alive	Treated BU AP at 18 months Treated HU and 6-MP Died of pneumonia	ND	Not treated Died of causes unrelated to CML process	Treated αINF and HU BMT (allo and auto) Alive	Treated αINF after achieving CR Alive	Treated HU BMT Alive

*CP, chronic phase; AP, accelerating phase; BC, blast crisis; ND, not described; αINF, alpha-interferon; BU, busulfan; HU, hydroxyurea; 6-MP, 6-mercaptopurine; BMT, bone marrow transplantation. The case described by Sawyers et al. [17] is excluded because of its lack of clinical data.
[a]Data in ALL phase. Basophilia (−) and monocytosis (−) in CP.

hand, the high percentage of immature granulocytes and low NAP score are compatible with CML, while basophilia is not prominent in general. Thus, m-BCR CML appears to represent a novel clinical entity as an atypical form of CML, in which $p190^{BCR\text{-}ABL}$ might induce preferential proliferation of both myeloid and monocytoid lineages.

Rapid progression to a hybrid type of blast crisis was observed in the present case. The blastic cells were equipped with both myeloid and B-lymphoid phenotypes, but were devoid of T-lymphoid markers. However, Southern blot analysis disclosed TCRβ and TCRγ gene rearrangements as well as deletions of immunoglobulin heavy chain and κ light chain. This discrepancy between phenotype and genotype may be due to deranged activation of recombinases, demonstrating lineage infidelity of the leukemic cells of this patient.

While BCR-ABL fusion event plays a crucial role in the pathogeny of Ph^+ CML and ALL, the molecular events that determine the phenotype of the disease remain to be clarified. A series of the reports on m-BCR CML including the present case and very recent report by Pane et al. on BCR-ABL chronic neutrophilic leukemia with c3a2 junction [22] may shed light on this problem; i.e., the phenotype of the disease may depend on the length of BCR domains of the hybrid BCR-ABL protein [3]. The residual biological activity of the fusion products may account for disease phenotype. Further accumulation and careful observation of these cases would be indispensable to make this hypothesis convincing.

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